IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TENNESSEE
WESTERN DIVISION

PATRICIA NOZINICH and PETER NOZINICH, Plaintiffs, vs. JOHNSON & JOHNSON, INC. and CENTOCOR, INC., Defendants.	)	No. 09-02105 DKV

ORDER GRANTING DEFENDANTS' MOTION TO EXCLUDE EXPERT TESTIMONY OF DR. TREW, GRANTING DEFENDANTS' MOTION FOR SUMMARY JUDGMENT, AND DENYING PLAINTIFFS' MOTION FOR PARTIAL SUMMARY JUDGMENT AS MOOT

This is a products liability case against the manufacturers, marketers, and distributers of the drug Remicade, generically known as Infliximab. The plaintiffs, Patricia and Peter Nozinich, allege that Patricia Nozinich developed multiple pulmonary emboli after receiving intravenous doses of Remicade. Dr. Judy Ash, one of Ms. Nozinich's treating physicians, prescribed Remicade to treat her rheumatoid arthritis.

Before the court is the April 7, 2011 motion of the defendants, Johnson & Johnson, Inc. and Centocor, Inc., to exclude the expert testimony of Dr. Gary F. Trew, the expert designated by the plaintiffs. (D.E. 85.) On April 29, 2011, the court initially granted the defendants' motion to exclude Dr. Trew on the grounds that the plaintiffs failed to respond to the motion. On May 3, 2011, the plaintiffs filed a motion to reconsider the court's

order. The court granted the plaintiffs' motion to reconsider on May 20, 2011, the plaintiffs filed a response in opposition to he motion, the defendants filed a reply, and a hearing was held June 21, 2011.

Also before the court is the April 7, 2011 motion of the defendants for summary judgment (D.E. 86) and the April 7, 2011 motion of the plaintiffs for partial summary judgment (D.E. 87). The parties have filed timely responses to both of these motions and replies to the responses.

For the reasons that follow, the defendants' motion to exclude the expert testimony of Dr. Trew is granted, the defendants' motion for summary judgment is granted, and the plaintiffs' motion for partial summary judgment is denied as moot.

I. UNDISPUTED FACTS

Ms. Nozinich was diagnosed with rheumatoid arthritis in 2004. (Pls.' Resp. to Defs.' Statement of Undisputed Facts, D.E. 130 ¶ 9.) During the course of her treatment for rheumatoid arthritis she was placed on a variety of medications, including Plaquenil, Bextra, Enbrel, Mobic, Celebrex, Methotrexate, and Arava. (*Id.* ¶ 11.) After Enbrel was discontinued in September 2007, Dr. Ash, Ms. Nozinich's treating physician for her rheumatoid arthritis, started her on Remicade infusions. Ms. Nozinich received four infusions of Remicade: the first infusion was administered on October 30, 2007; the second infusion was administered on November

27, 2007; the third infusion was administered on December 16, 2007; and the fourth infusion was administered on February 19, 2008. (*Id.* ¶¶ 13, 19.) While being treated with Remicade, Ms. Nozinich was still being treated with Celebrex and Methotrexate, both of which have an associated risk of pulmonary embolism. (*Id*. ¶ 14.) In addition, in November 2007, after her first treatment of Remicade, Ms. Nozinich and her husband drove from Coldwater, Mississippi to Pittsburgh, Pennsylvania (a fifteen hour automobile ride each way) to attend a funeral. (*Id*. ¶ 15.)

After receiving the first infusion, and prior to the second treatment, during the road trip in November 2007, Ms. Nozinich complained of shortness of breath and chest pain.[1] (*Id*. ¶ 16.) On January 15, 2008, Ms. Nozinich was admitted to Baptist Memorial Hospital in Memphis because of chest pain and shortness of breath, and she was diagnosed with and treated for bilateral pulmonary emboli. (*Id.* ¶ 17.) During her stay at Baptist Memorial Hospital,

[1] Ms. Nozinich claims that she first began experiencing chest pain and difficulty breathing following her first Remicade infusion but she does not specify the date. (Pls.' Resp. to Defs.' Statement of Undisputed Facts, D.E. 130, Ex. 12, Nozinich Dep. at 69:4.) The defendants claim that Ms. Nozinich's medical records reflect that she first experienced shortness of breath four months prior to her initial treatment with Remicade. (Aff. of Gary Epler, M.D., D.E. 84 at ¶ 11.) Dr. Trew's expert report indicates that Ms. Nozinich complained again about shortness of breath after her second Remicade infusion and that she experienced chest pain and increasing shortness of breath with exertion after her third Remicade infusion. (Pls.' Expert Witness Disclosure, D.E. 81-2 at 7.)

Ms. Nozinich was placed on the drug Coumadin to treat her pulmonary emboli. (*Id*. ¶ 18.)

Although Dr. Ash knew Ms. Nozinich had developed pulmonary emboli in January 2008, she administered a fourth infusion of Remicade on February 19, 2008 because she did not think pulmonary embolism was related to Remicade because the risk of pulmonary embolism was so low. (Defs.' Statement of Undisputed Facts, D.E. 86-6 ¶ 20, Ex. A, Dr. Ash's Dep. at 49:21-24, 50:1-16.) Ms. Nozinich did not develop a pulmonary embolism after the fourth infusion. While being treated with Remicade, Ms. Nozinich's rheumatoid arthritis symptoms improved. (Pls.' Resp. to Defs.' Statement of Undisputed Facts, D.E. 130 ¶ 21.)

Prior to administering Remicade initially and prior to the fourth infusion, Dr. Ash received information from Centocor on the occurrence of thrombotic events in patients being treated with Remicade. The information included Centocor's clinical trial data. Thrombotic events were reported as, or broken down into, seven individual events: thrombophlebitis,[2] phlebitis,[3] thrombophlebitis deep,[4] superficial thrombophlebitis,[5] thrombophlebitis deep leg,

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[2] Thrombophlebitis is vein inflammation due to a thrombus. LIPPINCOTT, WILLIAMS & WILKINS, STEDMAN'S MEDICAL DICTIONARY 409020 (27th ed. 2000).

[3] Phlebitis is inflammation of a vein. LIPPINCOTT, WILLIAMS & WILKINS, STEDMAN'S MEDICAL DICTIONARY 321330 (27th ed. 2000).

[4] Deep vein thrombosis is the formation of a blood clot in a vein deep inside a part of the body, usually the legs. MEDSCAPE

superficial leg thrombophlebitis, and pulmonary embolism. The study revealed that thrombophlebitis and pulmonary embolism both occurred at a rate equal to placebo. (Pls.' Resp. to Defs.' Statement of Undisputed Facts, D.E. 130 ¶ 20; Pls.' Statement of Undisputed Facts, D.E. 87-1 ¶ 33.) The following table was included in the information Centocor sent to Dr. Ash:

Table 1. Thrombotic disorders reported in patients treated with REMICADE in clinical trials

	Overall Incidence		Serious	
	REMICADE**	PCB*	REMICADE**	PCB*
Thrombophlebitis	0.1%	0.1%	0%	0%
Phlebitis	0.2%	0.1%	0%	0%
Thrombophlebitis Deep	0.1%	0.3%	0.1%	0.3%
Superficial Thrombophlebitis	0.1%	0%	0%	0%
Thrombophlebitis Deep Leg	0.1%	0.1%	0.1%	0.1%
Superficial Leg Thrombophlebitis	0.1%	0%	0%	0%
Pulmonary Embolism	0.2%	0.2%	0.2%	0.2%

*PCB = placebo; **REMICADE = Dosage groups Combined

REFERENCE, (last visited July 5, 2011), http://emedicine.medscape.com/article/463256-overview.

[5] Superficial thrombophlebitis affects veins near the skin surface. MEDSCAPE REFERENCE, (last visited July 5, 2011), http://emedicine.medscape.com/article/463256-overview.

(Pls.' Resp. to Defs.' Statement of Undisputed Facts, Ex. 2 Letter from Centocor, D.E. 130-2 at 3.) The table shows that thrombophlebitis deep actually occurred in the placebo group at a higher rate than with patients treated with Remicade.

Dr. Trew first met Ms. Nozinich on February 21, 2008, when she came in for an office visit for treatment as a follow-up to her hospitalization for her pulmonary emboli. (Pls.' Expert Witness Disclosure, D.E. 81-2 at 6.) Dr. Trew, her treating physician for the pulmonary emboli, has been designated as the expert witness for the plaintiffs. It is Dr. Trew's opinion that "the drug, Remicade, generically known as Infliximab, caused Ms. Nozinich's thrombotic event." (*Id*. at 6.) A "thrombotic event" is a blood clot in a blood vessel. *See generally* LIPPINCOTT, WILLIAMS & WILKINS, STEDMAN'S MEDICAL DICTIONARY 409020 (27th ed. 2000). In forming his opinion, Dr. Trew stated that he reviewed Ms. Nozinich's medical record several years prior to the introduction of Remicade and the immediate period surrounding the administration of the drug, the Infliximab drug information from UpToDate May 28, 2009, the February 26, 2008 letter from Centocor to Dr. Ash concerning thrombotic events and Remicade, and literature concerning Remicade and thrombotic events, consisting of ten case studies. (*Id.* at 8-9.)

As set forth in Dr. Trew's report, based on a review of her medical records, after Ms. Nozinich was diagnosed with rheumatoid

arthritis, Ms. Nozinich was started on Bextra, a non-steroidal anti-inflammatory drug (NSAID), and Enbrel, a drug classified as a tumor necrosis factor alpha blocker (an anti-TNF drug). (*Id.* at 6.) "She was continued on that combination into 2005 when Bextra was changed to another NSAID named Celebrex and Methotrexate, an anti-metabolite cancer treatment drug, was added to Enbrel. This was continued until 2006 when Arava, another type of anti-inflammatory drug was added to the regimen. In September 2007, Enbrel was discontinued. The Methotrexate, Arava, and Celebrex were continued and a drug called Remicade was started." (*Id.*) Remicade is another anti-TNF drug. (*Id.*) According to Dr. Trew, Ms. Nozinich's medications - Enbrel, Bextra, Celebrex, and Methotrexate - all carry a risk of pulmonary embolism. (Pls.' Resp to Defs.' Statement of Undisputed Facts, D.E. 103 ¶ 23.) Plus, according to Dr. Trew, Ms. Nozinich's medical conditions of rheumatoid arthritis, hyperlipidemia, and obesity are each associated with pulmonary embolism, thromboembolic events, and thrombotic events at a higher rate than would be expected in the general population. (Trew Dep., D.E. 81-1 at 69:3-6; 69:22-25; 71:8-12.)

The FDA approved Remicade for use with Crohn's disease in August 1998 and for use with rheumatoid arthritis in November 1999. (Pls.' Resp. to Defs.' Statement of Undisputed Facts, D.E. 130 ¶ 1.) Clinical studies conducted by Centocor and submitted to the

FDA determined that the occurrence of pulmonary embolism amongst rheumatoid arthritis patients is 0.197%. (*Id.* ¶ 5.) According to the affidavit testimony of Stella Jones, Vice-President of Global Regulatory Affairs, Immunology for Centocor, "[a]n estimated 1.1 million patients worldwide have received Remicade in a post-marketing setting from the time of its approval in 1998 to 2008. Approximately 564,000 of them were treated for rheumatoid arthritis and 362,000 for Chron's disease. During this period of time, 715 case of thromboembolic events were observed and reported to Centocor. The incidence rate of these events - which includes pulmonary embolism and other thrombotic events - among patients treated with Remicade is 0.065%." (Aff. of Stella Jones, Ph.D., D.E. 130-1 ¶¶ 9-10.)

Starting in 1999, the Remicade package insert listed pulmonary embolism as an adverse risk.[6] (Pls.' Resp. to Defs.' Statement of Undisputed Facts, D.E. 130 ¶ 6.) The Remicade package insert for 2007 provided the following in the Adverse Reaction section: "Other serious, medically relevant adverse events less than or equal to 0.2% or clinically significant adverse events by body system were as follows: . . . Vascular (Extracardiac): brain infarction,

[6] Stella Jones states in her affidavit that "[p]ulmonary embolism was described in the Remicade package insert as a possible adverse event from 2001 to 2009. In addition, peripheral ischemia, thrombophlebitis deep, and brain infarction were described in the Remicade labeling as possible adverse events for 2001 and 2009. (Jones Aff., D.E. 130-1 ¶ 9.)

pulmonary embolism, thrombophlebitis." (2007 Package Insert filed in Supp. of Pls.' Resp. to Defs.'Statement of Undisputed Facts, D.E. 132-3.) In April 2010, the FDA approved the removal of pulmonary embolism as an adverse event from the Remicade package insert, concluding that the data indicated that pulmonary embolism no longer met the necessary criteria to be included as an adverse drug reaction associated with taking Remicade. (Pls.' Resp. to Defs.' Statement of Undisputed Facts, D.E. 130 ¶ 8.)

Patients and doctors can submit reports to the FDA Medical Watch Program ("MedWatch reports") documenting symptoms or medical events which occur around the same time as the administration of a medicine by filling out a one-page form or reporting by telephone. Remicade labeling reflects data from MedWatch reports. Centocor submits Periodic Safety Update Reports (PSURs) to the FDA on a semi-annual basis to reflect any data on the incidence of thrombosis during the relevant six-month period. (Defs.' Resp. to Pls.' Mot. for Partial Summ. J., D.E. 115 at 3-4.) PSURs contain data from MedWatch reports, clinical trials, medical publications, registries and any other source of safety information. (*Id.*) UpToDate is a database of physician information on a variety of topics. The May 28, 2009 UpToDate Report lists the following thrombotic events as having a frequency of less than 5% for adults with rheumatoid arthritis receiving Remicade: pulmonary embolism

and thrombophlebitis (deep). (Pls.' Resp. to Defs.' Mot. in Limine to exclude the Test. of Dr. Gary F. Trew, D.E. 126-4.)

II. STANDARD OF REVIEW

A. Summary Judgment

Under Rule 56 of the Federal Rules of Civil Procedure, summary judgment is appropriate "if the pleadings, the discovery and disclosure of materials on file, and any affidavits show that there is no genuine issue as to any material fact and that the movant is entitled to judgment as a matter of law." FED. R. CIV. P. 56(c); *see also LaPointe v. United Autoworkers Local 600*, 8 F.3d 376, 378 (6th Cir. 1993); *Osborn v. Ashland County Bd. of Alcohol, Drug Addiction & Mental Health Servs.*, 979 F.2d 1131, 1133 (6th Cir. 1992) (per curiam). The party that moves for summary judgment has the burden of showing that there are no genuine issues of material fact at issue in the case. *LaPointe,* 8 F.3d at 378. This may be accomplished by pointing out to the court that the nonmoving party lacks evidence to support an essential element of its case. *Celotex Corp. v. Catrett*, 477 U.S. 317, 323 (1986); *Street v. J.C. Bradford & Co.*, 886 F.2d 1472, 1479 (6th Cir. 1989).

In response, the nonmoving party must go beyond the pleadings and present "significant probative evidence" to demonstrate that "there is [more than] some metaphysical doubt as to the material facts." *Moore v. Philip Morris Cos.*, 8 F.3d 335, 340 (6th Cir. 1993); *see also LaPointe*, 8 F.3d at 378. "[T]he mere existence of

some alleged factual dispute between the parties will not defeat an otherwise properly supported motion for summary judgment; the requirement is that there be no *genuine* issue of *material* fact." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247–48 (1986)(emphasis in original); *LaPointe*, 8 F.3d at 378.

In deciding a motion for summary judgment, "this [c]ourt must determine whether 'the evidence presents a sufficient disagreement to require submission to a jury or whether it is so one-sided that one party must prevail as a matter of law.'" *Patton v. Bearden*, 8 F.3d 343, 346 (6th Cir. 1993) (quoting *Anderson*, 477 U.S. at 251–52). The evidence, all facts, and any inferences that may permissibly be drawn from the facts must be viewed in the light most favorable to the nonmoving party. *Anderson*, 477 U.S. at 255; *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 587 (1986); *Patton*, 8 F.3d at 346; *60 Ivy St. Corp. v. Alexander*, 822 F.2d 1432, 1435 (6th Cir. 1987). However, to defeat a motion for summary judgment, "[t]he mere existence of a scintilla of evidence in support of the [nonmovant's] position will be insufficient; there must be evidence on which the jury could reasonably find for the [nonmovant]." *Anderson*, 477 U.S. at 252; *LaPointe*, 8 F.3d at 378. Finally, a district court considering a motion for summary judgment may not weigh evidence or make credibility determinations. *Anderson*, 477 U.S. at 255; *Adams v. Metiva*, 31 F.3d 375, 379 (6th Cir. 1994).

B. Admissibility of Expert Testimony

The party proffering expert testimony bears the burden of establishing its admissibility by "a 'preponderance of proof.'" *Coffey v. Dowley Mfg., Inc.*, 187 F. Supp. 2d 958, 970 (M.D. Tenn. 2002).

For an expert's testimony to be admissible, it must comport with the requires of Rule 702 of the Federal Rules of Evidence, as discussed and interpreted by the Supreme Court in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993) and *Pride v. BIC Corp.*, 218 F.3d 566, 577-78 (6th Cir. 2000). Rule 702 provides:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

FED. R. EVID. 702. Thus, expert testimony may only be admitted into evidence if: (1) the witness qualifies as an expert; (2) the methodology by which the expert reaches his or her conclusions is sufficiently reliable; and (3) the expert's testimony will assist the trier of fact to understand the evidence or determine a fact in issue. *Id.*; *Daubert*, 509 U.S. at 589-91.

Essentially, *Daubert* requires a two-step inquiry that involves an analysis of the "relevance and the reliability" of an expert's opinion. *Greenwell v. Boatwright*, 184 F.3d 492, 496 (6th Cir.

1999). The relevance step of the inquiry is designed to ensure that "there is a 'fit' between the testimony and the issue to be resolved by the trial." *Id.* (citing *United States v. Bonds*, 12 F.3d 540, 555 (6th Cir. 1993)). The reliability step focuses on the "methodology and principles" that form the basis for the testimony. *Id.*

III. ANALYSIS

In the present case, the defendants filed a motion for summary judgment and a corresponding motion in limine to exclude the expert testimony of Dr. Trew. In the defendants' motion for summary judgment, the defendants argue that the plaintiffs cannot prove general or specific causation because expert testimony is required to prove causation, and the plaintiffs only expert, Dr. Trew, is not qualified to give an opinion on causation, his opinion is unreliable, and his opinion is not relevant.

A. Expert Testimony Required on Causation

In a products liability action, a plaintiff must prove both general and specific causation. *See Downs v. Perstorp Components, Inc.*, 126 F. Supp. 2d 1090, 1095 (E.D. Tenn. 1999). General causation is "whether a substance is capable of causing a particular injury or condition in the general population," and specific causation is whether a product caused a particular person's alleged injury. *See Knight v. Kirby Inland Marine, Inc.*, 482 F.3d 347, 351 (5th Cir. 2007). When the issue of causation is

not within a lay person's knowledge, testimony of an expert witness is necessary. *See generally* FED. R. EVID. 702.

In the present case, the plaintiffs have only designated one expert, Dr. Trew, on the issue of causation. At the hearing, both sides agreed that if the court determines that Dr. Trew's expert testimony on causation is inadmissable, the plaintiffs will have failed to prove causation on any of their claims, and summary judgment in favor of the defendants would be appropriate on all the claims.

B. Admissibility of the Expert Testimony of Dr. Trew

1. *Dr. Trew's Qualifications*

The defendants argue that Dr. Trew lacks the requisite "knowledge, skill, experience, training or education" to qualify as an expert under Rule 702 to give testimony on the causal relationship between Remicade and Ms. Nozinich's pulmonary emboli for the following reasons: (1) he has never prescribed Remicade to any of his patients; (2) he has only treated one other patient, besides Ms. Nozinich, for pulmonary embolism while on an anti-TNF medication; (3) he has not published any literature or given any lectures on Remicade and/or pulmonary emboli in the past twenty years; (4) he never acquired or extensively read materials regarding Remicade prior to this litigation; and (5) he is not an expert on rheumatoid arthritis or hematology.

The defendants do not dispute that Dr. Trew is qualified based on his education, experience, and training to accurately diagnose and treat a patient with a thrombotic event; the defendants dispute that Dr. Trew has the ability to identify the cause and etiology of a thrombotic event, specifically a pulmonary embolism. (Defs.' Reply Mem., D.E. 140 at 2.) As the Sixth Circuit recently noted, "[M]ost treating physicians have more training and experience with diagnosis than etiology." *Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 673 (6th Cir. 2009).

Although Dr. Trew is not an expert in rheumatoid arthritis or hematology, he is a practicing board certified doctor specializing in pulmonology. Dr. Trew completed a fellowship in pulmonary medicine from 1974 to 1976. He has been board certified in internal medicine since 1983, in pulmonary disease since 1984, and in critical care medicine since 1991. Dr. Trew treated Ms. Nozinich for multiple pulmonary emboli during her hospital stay from January 15, 2008 until January 23, 2008. He personally observed Ms. Nozinich and the symptoms she was experiencing after her third Remicade infusion. The fact that Dr. Trew has never prescribed Remicade or published literature or lectured on Remicade does not disqualify him but may lessen the weight of his testimony. *See Davis v. Combustion Eng'g., Inc.*, 742 F.2d 916, 919 (6th Cir. 1984)("The fact that a proffered expert may be unfamiliar with pertinent statutory definitions or standards is not grounds for

disqualification. Such lack of familiarity affects witness' credibility, not his qualifications to testify.")

Even though Dr. Trew may have more training and experience in diagnosing and treating pulmonary emboli rather than determining the cause of the pulmonary emboli, the court cannot, based on the information provided, conclude that Dr Trew is not qualified to determine the cause of pulmonary emboli in a medically reliable manner. As such, the court finds that Dr. Trew's experience, knowledge, training, skill, and education qualify him to provide an expert opinion on causation in order to assist the jury in determining causation if the methodology he uses is scientifically and medically reliable.

2. *Reliability of Dr. Trew's Opinion*

Dr. Trew opined that Remicade caused Ms. Nozinich's "thrombotic event." Although Ms. Nozinich was diagnosed with pulmonary emboli, Dr. Trew was very careful to articulate that he was not saying that Remicade caused her pulmonary emboli but that Remicade caused Ms. Nozinich to suffer a thrombotic event that then caused her pulmonary emboli. As he explained in his deposition,

> If you look at my opinion, it nowhere ways that I'm blaming Remicade for pulmonary embolism. It says that I think Remicade caused her thrombotic event. The pulmonary embolism is just one type of a clot, and it doesn't matter if the clot is in a cavern or a sinus, if it's in the retinal vein, if it's in your leg. If it's an increased incident of clotting which is what we're trying to establish, I've gotten away from the pulmonary embolism studies.

(Trew Dep., D.E. 81-1 at 66:16-67:6.) Thus, in order to render a causation opinion, Dr. Trew conflated pulmonary embolism with the broader category of all thrombotic events.

The defendants argue that Dr. Trew's opinion lacks reliability because it is not based on an acceptable scientific methodology. In reaching his opinion, Dr. Trew relied on the process of differential diagnosis. The Sixth Circuit has recognized that differential diagnosis is a valid and reliable technique under *Daubert* for determining causation, *Best v. Lowes Home Centers*, 563 F.3d 171, 179 (6th Cir. 2009), and the defendants concede that differential diagnosis is a valid basis for a medical causation opinion if properly applied. (Defs.' Reply Mem., D.E. 140 at 1.) *See also Tamraz*, 620 F.3d at 674 (citing *Glaser v. Thompson Med. Co.*, 32 F.3d 969, 977 (6th Cir. 1994)); *Pluck v. BP Oil Pipeline Co.*, 640 F.3d 671, 678 (6th Cir. 2011).

"Differential diagnosis is '[t]he method by which a physician determines what disease process caused a patient's symptoms. The physician considers all relevant potential causes of the symptoms and then eliminates alternative causes based on a physical examination, clinical tests, and a thorough case history." *Best*, 563 F.3d at 178 (quoting *Hardyman v. Norfolk & W. Ry. Co.*, 243 F.3d 255, 260 (6th Cir. 2001)). "A medical-causation opinion in the form of a doctor's differential diagnosis is reliable and admissible where the doctor (1) objectively ascertains, to the

extent possible, the nature of the patient's injury, . . . (2) 'rules in' one or more causes of injury using a valid methodology, and (3) engages in 'standard diagnostic techniques by which doctors normally rule out alternative causes' to reach a conclusion as to which cause is most likely." *Id.* at 179 (quoting *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717 (3d Cir. 1994)).

Merely because an expert uses the acceptable differential diagnosis methodology, however, does not mean his opinion is reliable. *Tamraz*, 620 F.3d 665, 675 ("[n]ot every opinion that is reached via a differential-diagnosis method will meet the standard of reliability required by Daubert")(quoting *Best*, 563 F.3d at 179). The court must still determine if the expert relied on scientifically valid bases as to which possible causes are "ruled in" and "ruled out."

Dr. Trew was Ms. Nozinich's treating physician for her pulmonary emboli; the defendants do not dispute that Dr. Trew objectively ascertained the nature of Ms. Nozinich's injury. Thus, the court finds that the first stage of Dr. Trew's differential diagnosis to be reliable. The critical issues are whether Dr. Trew reliably "ruled in" causes and "ruled out" causes in the second and third phase of his differential diagnosis.

a. Reliability of Dr. Trew's Ruling-In Stage of Differential Diagnosis

In determining possible different causes of Ms. Nozinich's pulmonary emboli, Dr. Trew "ruled-in" Remicade, obesity,

hyperlipidemia, rheumatoid arthritis, extended travel, and Ms. Nozinich's other medications including specifically Methotrexate, Enbrel, and Celebrex.[7] The defendants argue that Dr. Trew erroneously "ruled-in" Remicade because the literature upon which he relied does not support the conclusion that Remicade is capable of causing pulmonary embolism.

What exactly Dr. Trew relied upon to "rule-in" Remicade as one of the possible causes of Ms. Nozinich's "thrombotic event" is somewhat confusing. In his written report, Dr. Trew stated that in reaching his opinion, he reviewed Ms. Nozinich's medical records several years prior to the introduction of Remicade and the immediate period surrounding the administration of the drug, her hospital records from Baptist Hospital from January 15 to January 21, 2008, the Infliximab drug information from UptoDate May 28, 2009, the February 26, 2008 letter from Centocor to Dr. Ash concerning thrombotic events and Remicade, and ten articles discussing the use of Remicade in treating various diseases and the occurrence of various types of thrombotic events, most of which were individual case reports. (Trew Dep., D.E. 81-1 at 38-40.) In his deposition, Dr. Trew testified that after he reached his opinion and signed his report, he reviewed the following information which he relied on to "rule-in" Remicade as one of the

[7] Dr. Trew also ruled in hypercoaguability but ruled it out based on a clinical test performed to establish Ms. Nozinich's hypercoaguability profile.

possible causes of Ms. Nozinich's pulmonary emboli: MedWatch reports from 1999 to 2002 provided to him by plaintiffs' counsel of which he found 60 to be suggestive, UpToDate reports, the labels from Remicade for the past ten years, specifically for the past three years, PSURs from 2001 to 2006 concerning thromboembolic events provided to him by plaintiffs' counsel, and two articles from 2006 and 2007 "eluding to ineptness in the FDA's ability to handle adverse events and reports." (Trew Dep., D.E. 81-1 at 8-9.) He also testified that he relied on the 2007 Remicade package insert and his experience with one other patient in 2002 who experienced a pulmonary embolism while taking another anti-TNF drug, Enbrel. (Trew Dep., D.E. 81-1 at 17-18.) In addition, he testified that he relied on the temporal proximity between Ms. Nozinich's infusions with Remicade and her development of pulmonary emboli. (Trew Dep., D.E. 81-1 at 48, 69-70.) He did not rely on any study, article, or paper which concluded that Remicade is associated with an increased risk of a thrombotic event. He did not rely on or find in his medical literature search any epidemiological study which showed an increased risk of thromboembolic events in persons taking Remicade. (Trew Dep., D.E. 81-1 at 43.)

(i) *Case Reports, MedWatch Reports, and PSURs as Reliable Evidence*

Case reports, MedWatch reports, and PSURs are based on observations made by doctors or patients when an individual

demonstrates adverse symptoms around the same time a medication is prescribed. Courts have found that these reports are unreliable because they are an uncontrolled collection of perceived adverse reactions.[8] *See, e.g., McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1250 (11th Cir. 2005)("[u]ncontrolled anecdotal information offers one of the least reliable sources to justify opinions about both general and individual causation"). As the district court in New York observed, adverse reaction reports "neither confir[m] nor den[y] that there is any relationship" between the medication and symptoms. *Saari v. Merck & Co., Inc.*, 961 F. Supp. 387, 394 & 398 (N.D.N.Y. 1997); *see also Goldstein v. Centocor*, 2009 WL 275322, *1 (11th Cir. Feb. 5, 2009)(excluding MedWatch reports under FED. R. EVID. 403). Case reports "contain very basic information, often omitting patient histories, descriptions of the course of treatment, and reasoning to exclude other possible causes." *Ervin v. Johnson & Johnson, Inc. and Centocor, Inc.*, 2006 WL 1529582, *6 (S.D. Ind. May 30, 2006). Many case reports do not attempt to rule-out alternative causes and provide little analysis. *Id.*

Here, none of the ten case reports relied on by Dr. Trew actually attributed any causal relationship between the use of Remicade and a thrombotic event. (Trew Dep., D.E. 81-1 at 81-96.) At best, they state the temporal relationship of a thrombotic event

[8] The plaintiffs cited no case authority upholding the use of case reports or MedWatch reports to prove causation.

to the use of Remicade raises concern as a possible related complication. Indeed, two of the case reports support the position that Remicade is not associated with pulmonary embolism. (Trew Dep., D.E. 81-1 at 97-99, 104-16 (ten-year case study of 750 patients who received Remicade for Inflammatory Bowel Disease and only one report of a pulmonary embolism).) Regardless, the plaintiffs now take the position in their brief that "Dr. Trew did not rely on these case reports to render his opinion." (Pls.' Resp., D.E. 126 at 12-13.)

Plaintiffs' counsel provided Dr. Trew a group of MedWatch reports from 1999 to 2002, which are, in essence, adverse reaction reports or case reports. From these, Dr. Trew threw out some and "came up with sixty that [he] could stay with." (Trew Dep., D.E. 81-1 at 146:18-19.) These he described as 60 clear incidences of pulmonary embolism with Remicade from 1999 to 2002. (Trew Dep., D.E. 81-1 at 146-147.) Dr. Trew, however, did not provide the number of patients who received Remicade over that period of time from which one could calculate the incidence rate, nor did Dr. Trew analyze the MedWatch reports for comorbidities or other potential causes. Thus, the MedWatch reports provide no meaningful and reliable data.

PSURs are periodic summaries of the MedWatch reports. Without any basis, Dr. Trew surmised in his deposition that Centocor failed to include all Medwatch reports in its six-month PSURs to the FDA.

(Trew Dep., D.E. 18-1 at 21-22.) Because PSURs are merely amalgamations of case reports, they are no more reliable than the underlying data.

Thus, the court finds the case reports, MedWatch reports, and PSURs unreliable and insufficient to substantiate Dr. Trew's conclusion that Remicade can cause thrombotic events in general, and Ms. Nozinich's pulmonary emboli specifically.

(ii) *UpToDate Reports as Reliable Evidence*

UpToDate is a database of physician information on a variety of topics. In his deposition, Dr. Trew testified to his subjective opinion that UpToDate reports are more reliable than the labels and clinical studies because the company does not provide the information. (Trew Dep., D.E. 81-1 at 21-22.) The May 2009 UpToDate reports show that pulmonary embolism and thrombophlebitis (deep) are noted as adverse reactions to Remicade in less than 5% of adults with rheumatoid arthritis. (D.E. 133-5 at 3.)

Dr. Trew surmised that if the May 2009 UpToDate reported the pulmonary embolism and thrombophlebitis (deep) at less than 5% then the incident rate must be 4% because in the UpToDate report in other areas, things are listed at 3%. (Trew Dep., D.E. 81-1 at 21, 111-112.) From that he concluded thrombotic events occur at 20 to 24 times the rate reported on the label:

> This one implied to me that it is above 4 percent or they would say it was less than 4 percent. And it would show a 20 to 24 times the rate that's admitted to in the current Remicade label.

(Trew Dep., D.E. 81-1 at 112.) Dr. Trew's belief that the occurrence rate of thrombotic events is actually 4% is simply based on unsupported speculation on his part. In addition, Dr. Trew has not explained the mathematical methodology for his calculation that the true incident rate of thrombotic events is 20 to 24 times higher than the label reports. Dr. Trew provides no reliable basis for his calculations, and therefore the UpToDate is not a reliable basis for his opinion. *See Pluck v. BP Oil Pipeline Co.*, 640 F.3d 671, 679 (affirming the exclusion of a proffered expert witness' causation opinion where he could not "explain the methodology for his calculations"); *see also Tamraz*, 620 F.3d 665, 670.

(iii) *The Remicade Package Insert as Reliable Evidence*

Dr. Trew also relied on the defendant's own package inserts for Remicade in support of his opinion that Remicade should be "ruled-in." Dr. Trew reasoned that if an adverse event is listed in the package insert for Remicade, then *ipso facto*, the rate of incidence of that adverse event exceeds the placebo rate. (Trew Dep., D.E. 81-1 at 32-34.) In reaching this conclusion, Dr. Trew relied on the 2008 FDA Guidance For Industry labeling document which listed seven factors as important for labeling, one of which was the extent to which the adverse event rate of the drug exceeds the placebo rate. (Trew Dep., D.E. 81-1 at 32.) Because thrombophlebitis was included in the 2010 label even though pulmonary embolism was not, he concluded the rate of

thrombophlebitis in rheumatoid patients treated with Remicade exceeded the placebo rate, and therefore the rate of thrombotic events in patients treated with Remicade exceeds the placebo rate. (Trew Dep., D.E. 81-1 at 33.) When questioned about when the 2008 guidance document for labeling became effective, he had no idea when it was required to take effect. (Trew Dep., D.E. 81-1 at 33.) He could not explain why pulmonary embolism was not included in the 2010 and 2011 package inserts.

For 2007, the package insert listed both pulmonary embolism and thrombophlebitis at less than 0.2% rate of incidence based on clinical studies conducted by Centocor. (*See* discussion of clinical studies, *infra*, pp. 4-5.) Even though the clinical studies revealed that the overall incidence rate of pulmonary embolism and thrombophlebitis in patients receiving Remicade equal the placebo rate, Dr. Trew added the rates for all six categories of thrombotic events and concluded that the overall incident rate of "thrombotic events" exceeded the placebo rate by one tenth of one percent. In doing so and in order to reach his conclusion, Dr. Trew overlooked or downplayed any distinction between the types of thrombotic events. Plus, he ignored and gave no weight to the fact that pulmonary embolism was not included as an adverse event in the 2010 product label.

Further, adverse events included in a product's labeling cannot be used as evidence of causation because the FDA's standard

when evaluating drugs differs from the standard for establishing causation in tort actions. *See* 21 C.F.R. § 201.57(c)(6)(i)("[T]he labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established."); *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)("The FDA will remove drugs from the marketplace upon a lesser showing of harm to the public than . . . standards used to assess tort liability. The methodology employed by a government agency results from the preventive perspective that the agencies adopt in order to reduce public exposure to harmful substances.")(internal quotations omitted). Thus, the product labels do not provide a reliable basis for "ruling in" Remicade or concluding that Remicade could cause a pulmonary embolism.

(iv) *Dr. Trew's Personal Experience as Reliable Evidence*

Dr. Trew testified that in his practice, he had treated one other patient, who suffered a pulmonary embolism while taking another anti-TNF medication, Enbrel. Indeed, Ms. Nozinich had taken Enbrel from 2004 before discontinuing it in September 2007, one month before Ms. Nozinich claims she first developed symptoms of a pulmonary embolism. Dr. Trew fails to explain, however, any basis for his belief that Enbrel caused his other patient's pulmonary embolism other than his subjective belief, whether there

were other compounding factors or potential causes of his other patient's pulmonary embolism, and why he then "ruled-out" Enbrel as a possible cause of Ms. Nozinich's pulmonary embolism. Nor does he say how many patients he has treated who took anti-TNF medications and who did not suffer from a pulmonary embolism or other thrombotic event. Thus, Dr. Trew's clinical experience does not constitute a reliable basis for "ruling-in" Remicade as a potential cause of pulmonary embolism.

(v) *Idiopathic Causes*

In his deposition, Dr. Trew acknowledged that about "a third of pulmonary embolism diagnosed in this country every year are idiopathic," meaning no known cause. (Trew Dep., D.E. 81-1 at 68.) Dr. Trew, however, did not "rule-in" idiopathic as a possible cause because there were several other possible causes. (Trew Dep., D.E. 81-1 at 68-69.) In *Tamraz*, the Sixth Circuit found fault with the expert's differential diagnosis when he did not consider idiopathic causes when it accounted for the vast majority of the disease at issue. *Tamraz*, 620 F.3d at 675. The court finds, therefore, that Dr. Trew's "ruling in" stage of his differential diagnosis was flawed.

In sum, Dr. Trew's decision to "rule-in" Remicade is based on unreliable data demonstrating an insignificant occurrence rate. Further, Dr. Trew did not provide any epidemiological studies or papers or articles which concluded that Remicade increases the risk

of thrombotic events in general or pulmonary emboli specifically in patients with rheumatoid arthritis. As such, the court finds that Dr. Trew's application of the differential diagnosis technique is flawed and fails to meet the standards set out in *Daubert*.

b. Reliability of Dr. Trew's "Ruling-Out" Stage of Differential Diagnosis

Even if Dr. Trew had reliably "ruled-in" Remicade as a cause of Ms. Nozinich's pulmonary embolism, he failed to reliably "rule-out" other causes. In a differential diagnosis, after "ruling-in" all possible causes of an individual's symptoms, the expert's next step is to "rule-out" each possible cause based on the plaintiff's individual case. In his expert report, Dr. Trew stated that there were a number of known precipitating factors for the abnormal development of blood clots or thrombi, such as prolonged period of sitting, estrogen therapy, cancers, but that Ms. Nozinich had none of these risks. (D.E. 81-2 at 11.)

Dr. Trew "ruled-out" the factor of prolonged period of sitting because Ms. Nozinich's fifteen-hour car trip to Pittsburgh occurred six weeks before her thrombotic event. (D.E. 126-3 at 26.) Dr. Trew pointed out that from his experience, patients who suffer from a thrombotic event as the result of travel immediately develop symptoms.[9]

[9] It should be noted that Ms. Nozinich traveled in November 2007, after which she complained that her shortness of breath increased.

Dr. Trew also noted that Ms. Nozinich was on several drugs that are known to cause thrombotic events, such as Celebrex, Methotrexate, and Enbrel, at the time she developed pulmonary emboli, (Trew Dep., D.E. 81-1 at 72), but "ruled-out" these medications because Ms. Nozinich had been on them since 2004 with no signs or symptoms of clotting abnormalities. Dr. Trew failed to consider, however, any increased risk of thrombotic events based on chronic or long-time use of these drugs and simply "ruled-out" these drugs based on the temporal proximity of the use of Remicade. (Trew Dep., D.E. 81-1 at 73-74.) Without such consideration, the court cannot conclude that Dr. Trew reliably "ruled-out" these medications as potential causes.

Dr. Trew also "ruled-out" obesity, hyperlipidemia, and rheumatoid arthritis, even though these conditions have been proven to cause thrombotic events, based on the fact that Ms. Nozinich had been living with these risk factors before and after the onset of her pulmonary embolism. (Pl.'s Resp., D.E. 126-3 at 14-17.) With respect to Ms. Nozinich's obesity, Dr. Trew admitted that the incidence of blood clots increased over time in obese patients, which meant that Ms. Nozinich had a greater risk of developing a blood clot in 2007 than she did in earlier years. (Trew Dep., D.E. 81-1 at 88:17-89:9.) Yet, ignoring this increased risk over time, Dr. Trew proceeded to "rule-out" obesity as a possible cause with

no explanation other than temporal proximity of the administration of Remicade. (Trew Dep., D.E. 81-1 at 74.)

Throughout the "ruling-out" stage of differential diagnosis, Dr. Trew repeatedly based his conclusions to "rule out" other possible causes primarily on the temporal proximity of the administration of Remicade. Dr. Trew "ruled-out" Ms. Nozinich's car trip because it took place six weeks before her pulmonary embolism occurred; he "ruled-out" other medications without considering increased risk of thrombotic events based on chronic use because of the temporal proximity of the use of Remicade; he "ruled-out" obesity, rheumatoid arthritis, and hyperlipidemia without considering increased risk of pulmonary embolism over time and with advanced age, because of the temporal proximity of the use of Remicade. Thus, Dr. Trew opined that Remicade caused Ms. Nozinich's pulmonary embolism based on the temporal proximity between Ms. Nozinich's symptoms and her infusions of Remicade. Although the Sixth Circuit considers temporal proximity as a factor when determining causation, "the mere existence of temporal relationship between taking a medicine and the onset of symptoms does not show a sufficient causal relationship." *See Ervin v. Johnson & Johnson, Inc.*, 492 F.3d 901, 904-05 (7th Cir. 2007).

Accordingly, the court finds that the flaws in Dr. Trew's differential diagnosis render his opinion on causation unreliable,

and therefore his testimony fails to meet the standards set out in *Daubert*.

III. CONCLUSION

Based on the reasons stated above, the court grants the defendants' motion in limine to exclude the testimony of Dr. Trew and grants the defendants' motion for summary judgment. Because the defendants are entitled to summary judgment, the plaintiffs' motion for partial summary judgment is denied as moot.

IT IS SO ORDERED, this 6th day of July, 2011.

s/ Diane K. Vescovo
DIANE K. VESCOVO
UNITED STATES MAGISTRATE JUDGE